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<p>(21) International Application Number: PCT/GB95/01465 (22) International Filing Date: 22 June 1995 (22.06.95) (30) Priority Data: 9412514.3 22 June 1994 (22.06.94) GB 9506107.3 24 March 1995 (24.03.95) GB (71) Applicant (for all designated States except US): BRITISH BIOTECH PHARMACEUTICALS LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): MILLER, Andrew [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). WHITTAKER, Mark [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). BECKETT, Raymond, Paul [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). (74) Agent: WALLS, Alan, J.; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).</p>		<p>(81) Designated States: AU, BR, CA, CN, CZ, DE, FI, GB, HU, JP, KR, NO, NZ, PL, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.</p>
<p>(54) Title: METALLOPROTEINASE INHIBITORS</p> <p>(57) Abstract</p> <p>Compounds of general formula (II), wherein X is a hydroxamic or carboxylic acid group, Y is sulphonyl and R₁ and R₂ as defined in the claims are matrix metalloproteinase inhibitors.</p> <div style="text-align: center;"> $\begin{array}{c} R_2 - N - Y - Z \\ \\ R_1 - C - X \end{array} \quad (II)$ </div>		

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Metalloproteinase Inhibitors

The present invention relates to therapeutically active hydroxamic acid and carboxylic acid derivatives, to processes for their preparation, to pharmaceutical compositions containing them, and to the use of such compounds in medicine. In particular, the compounds are inhibitors of metalloproteinases involved in tissue degradation.

Background to the Invention

Metalloproteinase Inhibitors

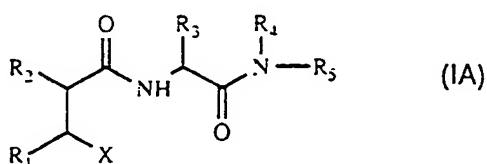
Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown such as collagenase, stromelysin and gelatinase (known as "matrix metalloproteinases", and herein referred to as MMPs) are thought to be potentially useful for the treatment or prophylaxis of conditions involving such tissue breakdown, for example rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal epidermal or gastric ulceration, and tumour metastasis, invasion and growth. MMP inhibitors are also of potential value in the treatment of neuroinflammatory disorders, including those involving myelin degradation, for example multiple sclerosis, as well as in the management of angiogenesis dependent diseases, which include arthritic conditions and solid tumour growth as well as psoriasis, proliferative retinopathies, neovascular glaucoma, ocular tumours, angiofibromas and hemangiomas.

Metalloproteinases are characterised by the presence in the structure of a zinc(II) ion at the active site. It is now known that there exists a range of metalloproteinase enzymes that includes fibroblast collagenase (Type 1), PMN-collagenase, 72 kDa-gelatinase, 92 kDa-gelatinase, stromelysin, stromelysin-2 and PUMP-1 (L.M. Matrisian, *Trends in Genetics*, 1990, 6, 121-125).

Many known MMP inhibitors are peptide derivatives, based on naturally occurring amino acids, and are analogues of the cleavage site in the collagen molecule. A recent paper by Chapman et al (J. Med. Chem. 1993, 36, 4293-4301) reports some

general structure/activity findings in a series of N-carboxyalkyl peptides. Other known MMP inhibitors are less peptidic in structure, and may more properly be viewed as pseudopeptides or peptide mimetics. Such compounds usually have a functional group capable of binding to the zinc (II) site in the MMP, and known classes include those in which the zinc binding group is a hydroxamic acid, carboxylic acid, sulphhydryl, and oxygenated phosphorus (eg phosphinic acid and phosphonic acid) groups.

Two known classes of pseudopeptide or peptide mimetic MMP inhibitors have a hydroxamic acid group and a carboxylic group respectively as their zinc binding groups. With a few exceptions, such known MMPs may be represented by the structural formula (IA)



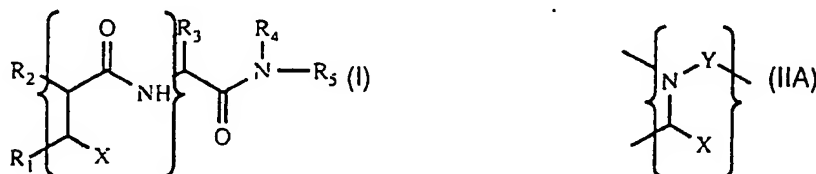
in which X is the zinc binding hydroxamic acid (-CONHOH) or carboxylic acid (-COOH) group and the groups R₁ to R₅ are variable in accordance with the specific prior art disclosures of such compounds. The following patent publications disclose hydroxamic acid-based and/or carboxylic acid-based MMP inhibitors:

US 4599361	(Searle)
EP-A-2321081	(ICI)
EP-A-0236872	(Roche)
EP-A-0274453	(Bellon)
WO 90/05716	(British Bio-technology)
WO 90/05719	(British Bio-technology)
WO 91/02716	(British Bio-technology)
WO 92/09563	(Glycomed)
US 5183900	(Glycomed)
US 5270326	(Glycomed)
WO 92/17460	(SmithKline Beecham)

EP-A-0489577	(Celltech)
EP-A-0489579	(Celltech)
EP-A-0497192	(Roche)
US 5256657	(Sterling Winthrop)
WO 92/13831	(British Bio-technology)
WO 92/22523	(Research Corporation Technologies)
WO 93/09090	(Yamanouchi)
WO 93/09097	(Sankyo)
WO 93/20047	(British Bio-technology)
WO 93/24449	(Celltech)
WO 93/24475	(Celltech)
EP-A-0574758	(Roche)
WO 94/02447	(British Biotech)
WO 94/02446	(British Biotech)

Brief Description of the Invention

The present invention makes available a new class of MMP inhibitors, related to those of general formula (I) known from the patent publications listed above in that they also have hydroxamic acid or carboxylic acid zinc binding groups, but incorporating a major structural change in the "backbone". In the compounds of this invention the portion of the "backbone" corresponding to the bracketed portion of general formula (I) may be represented by partial formula (IIA):



where Y is a carbonyl (-C(=O)-) or sulphonyl (-S(=O)₂-) group.

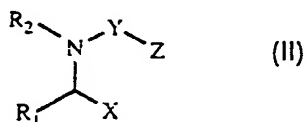
A further advantage of compounds of the present invention is that they inhibit the production of the pro-inflammatory cytokine TNF.

Related Patent Publication

EP-A-0606046 (Ciba-Geigy), published 13th July 1994 discloses compounds also having the partial structure (IIA) where Y is a sulphonyl group.

Detailed Description of the Invention

The present invention provides a compound of general formula (II)



wherein

X represents a -CO₂H or -CONHOH group;

R₁ represents:

(i) the characterising side chain of a natural or non-natural alpha amino acid, in which any functional group present may be protected;

R₂ represents a group Z¹-Q-W- where Z¹ represents hydrogen or an optionally substituted aryl, heteroaryl, non-aromatic heterocyclyl, cycloalkyl, or cycloalkenyl group, and

(i) -Q-W- taken together represent a bond or

(ii) Q represents -O- or -S- and W represents a divalent C₁-C₂₀ straight or branched alkyl or C₂-C₂₀ alkenyl group which

(a) may be interrupted by one or more non-adjacent ether or thioether linkages or -N(R_x)- groups wherein R_x is hydrogen, or C₁-C₆ alkyl, and/or

(b) may carry one or more substituents selected from -OH, -SH,

-O(Alk), -S(Alk), halogen, -NH₂, -NH(Alk), -N(Alk)₂, -CO₂H, -CO₂(Alk), -CO(Alk), -CHO, -CONH₂, -CONH(Alk), -CON(Alk)₂, -(Alk)OH, -(Alk)SH, and -NHCO(Alk) where Alk represents C₁-C₆ alkyl, or

(iii) Q represents a bond and W represents a divalent C₉-C₂₀ straight or branched alkyl or C₂-C₂₀ alkenyl group which

(a) may be interrupted by one or more non-adjacent ether or thioether linkages or -N(R_x)- groups wherein R_x is hydrogen, or C₁-C₆ alkyl, and/or

(b) may carry one or more substituents selected from -OH, -SH, -O(Alk), -S(Alk), halogen, -NH₂, -NH(Alk), -N(Alk)₂, -CO₂H, -CO₂(Alk), -CO(Alk), -CHO, -CONH₂, -CONH(Alk), -CON(Alk)₂, -(Alk)OH, -(Alk)SH, and -NHCO(Alk) where Alk represents C₁-C₆ alkyl, or

(iv) Q represents a bond and W represents a divalent C₁-C₈ straight or branched alkyl group which

(a) carries one or more substituents selected from -SH, -CO₂H, -CO₂(Alk), -CHO, -CONH₂, -CONH(Alk), -CON(Alk)₂, and -(Alk)SH, where Alk represents C₁-C₆ alkyl, and

(b) (in the case where W is C₂-C₈) may be interrupted by one or more non-adjacent ether or thioether linkages or -N(R_x)- groups wherein R_x is hydrogen, or C₁-C₆ alkyl;

Y represents a sulphonyl (-SO₂-) group; and

Z represents an optionally substituted aryl, or heteroaryl group;

or a salt, hydrate or solvate thereof.

A particular sub-set of the compounds of the present invention are those of formula (II) above wherein R₂ represents

(i) a group Ar-Q-W- in which Ar represents optionally substituted aryl or heteroaryl, Q represents -O- or -S-, and W represents a divalent C₁-C₂₀ straight or branched chain alkyl moiety which may carry one or more substituents selected from OH, OMe, halogen, NH₂, NMeH, NMe₂, CO₂H, CO₂Me, COMe, CHO, CONH₂, CONHMe, CONMe₂, CH₂OH, NHCOMe; or

(ii) a group Ar-Q-W- in which Ar represents optionally substituted aryl or heteroaryl, Q represents a bond, and W represents a divalent C₉-C₂₀ straight or branched chain alkyl moiety may carry one or more substituents selected from OH, OMe, halogen, NH₂, NMeH, NMe₂, CO₂H, CO₂Me, COMe, CHO, CONH₂, CONHMe, CONMe₂, CH₂OH, NHCOMe; or

(iii) a group Ar-Q-W- in which Ar represents optionally substituted aryl or heteroaryl, Q represents a bond, and W represents a divalent C₁-C₈ straight or branched chain alkyl moiety which carries one or more substituents selected from -CO₂H, -CO₂Me, -CHO, -CONH₂, -CONHMe, and -CONMe₂; or

(v) a cycloalkenyl(C₁-C₆)alkyl group; or

(vi) a linear saturated C₉-C₂₀ or unsaturated C₂-C₂₀ hydrocarbon chain, which chain

(a) may be interrupted by one or more non-adjacent -O- or -S- atoms or -N(R_x)- groups wherein R_x is hydrogen, methyl or ethyl, and/or

(b) may be substituted with one or more groups selected from (C₁-C₆)alkyl, OH, OMe, halogen, NH₂, NMeH, NMe₂, CO₂H, CO₂Me,

COMe, CHO, CONH₂, CONHMe, CONMe₂, CH₂OH, NHCOMe,

provided that the maximum length of the chain is no more than 28 C, O, S and N atoms; or

(vii) a linear saturated C₂-C₈ hydrocarbon chain, which chain

(a) is substituted with one or more groups selected from -CO₂H, -CO₂Me, -CHO, -CONH₂, -CONHMe, and -CONMe₂, and

(b) may be interrupted by one or more non-adjacent -O- or -S- atoms or -N(R_x)- groups wherein R_x is hydrogen, methyl or ethyl,

provided that the maximum length of the chain is no more than 28 C, O, S and N atoms.

A further particular sub-set of the compounds of the present invention are those of formula (II) above wherein R₂ represents

(i) a cycloalkenyl(C₁-C₆)alkyl group, or

(ii) a linear saturated C₂-C₈ hydrocarbon chain, which chain

(a) may be interrupted by one or more non-adjacent -O- or -S- atoms or -N(R_x)- groups wherein R_x is hydrogen, methyl or ethyl, and

(b) is substituted with one or more groups selected from -CO₂H, -CO₂Me, -CHO, -CONH₂, -CONHMe, and -CONMe₂, or

(iii) a linear saturated C₉-C₂₀ or unsaturated C₂-C₂₀ hydrocarbon chain, which chain

(a) may be interrupted by one or more non-adjacent -O- or -S- atoms

or -N(R_x)- groups wherein R_x is hydrogen, methyl or ethyl, and/or

(b) may be substituted with one or more groups selected from (C₁-C₆)alkyl, OH, OMe, halogen, NH₂, NMeH, NMe₂, CO₂H, CO₂Me, COMe, CHO, CONH₂, CONHMe, CONMe₂, CH₂OH, NHCOMe,

provided that the maximum length of the chain is no more than 28 C, O, S and N atoms,

As used herein, the term "side chain of a natural or non-natural alpha amino acid" means the group R in a natural or non-natural amino acid of formula H₂N-CH(R)-COOH.

Examples of side chains of natural alpha amino acids include those of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glycine, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α -aminoadipic acid, α -amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α -methylserine, ornithine, pipecolic acid, and thyroxine.

Examples of side chains of non-natural alpha amino acids include:

(a) a hydrocarbon group -CR₉R₁₀R₁₁ in which each of R₉, R₁₀ and R₁₁ is independently hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, phenyl(C₁-C₆)alkyl; or R₉ and R₁₀ together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or R₉, R₁₀ and R₁₁ together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl);

or (b) a group -CR₁₂R₁₃R₁₄ in which each of R₁₂ and R₁₃ is independently (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, phenyl(C₁-C₆)alkyl, O(C₁-C₆)alkyl, S(C₁-C₆)alkyl, OH, SH, OPh, OCH₂Ph, SPh, SCH₂Ph, halogen, CN,

CO₂H, (C₁-C₄)perfluoroalkyl, CH₂OH, CO₂(C₁-C₆)alkyl, or a group phenyl or heteroaryl which is optionally substituted by one or more substituents independently selected from hydrogen, hydroxyl, halogen, CN, CO₂H, CO₂(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CONH(C₁-C₆alkyl)₂, CHO, CH₂OH, (C₁-C₄)perfluoroalkyl, O(C₁-C₆)alkyl, S(C₁-C₆)alkyl, SO(C₁-C₆)alkyl, SO₂(C₁-C₆)alkyl, NO₂, NH₂, NH(C₁-C₆)alkyl, N((C₁-C₆)alkyl)₂, NHCO(C₁-C₆)alkyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, C₄-C₈cycloalkenyl, phenyl or benzyl; and R₁₄ is hydrogen, OH, SH, OPh, OCH₂Ph, SPh, SCH₂Ph, halogen, CN, CO₂H, (C₁-C₄)perfluoroalkyl, CH₂OH, CO₂(C₁-C₆)alkyl, or a group phenyl or heteroaryl which is optionally substituted by one or more substituents independently selected from hydrogen, hydroxyl, halogen, CN, CO₂H, CO₂(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CONH(C₁-C₆alkyl)₂, CHO, CH₂OH, (C₁-C₄)perfluoroalkyl, O(C₁-C₆)alkyl, S(C₁-C₆)alkyl, SO(C₁-C₆)alkyl, SO₂(C₁-C₆)alkyl, NO₂, NH₂, NH(C₁-C₆)alkyl, N((C₁-C₆)alkyl)₂, NHCO(C₁-C₆)alkyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, C₄-C₈cycloalkenyl, phenyl or benzyl; or R₁₂ and R₁₃ together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring,

Functional groups in the amino acid side chains may be protected; for example carboxyl groups may be esterified (for example as a C₁-C₆ alkyl ester), amino groups may be converted to amides (for example as a COC₁-C₆ alkyl amide) or carbamates (for example as a C(=O)OC₁-C₆ alkyl or C(=O)OCH₂Ph carbamate), hydroxyl groups may be converted to ethers (for example a C₁-C₆ alkyl or a (C₁-C₆ alkyl)phenyl ether) or esters (for example a C(=O)C₁-C₆ alkyl ester) and thiol groups may be converted to thioethers (for example a C₁-C₆ alkyl thioether) or thioesters (for example a C(=O)C₁-C₆ alkyl thioester).

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "cycloalkenyl" means an unsaturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. In the case of cycloalkenyl rings of from 5-8 carbon atoms, the ring may contain more than one double bond.

The unqualified term "heterocyclyl" or "heterocyclic" refers to a 5-8 membered heterocyclic ring containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzene ring, including for example, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperizinyl, indolyl, benzimidazole, maleimido, succinimido, phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl and 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, naphththalimido (ie 1,3-dihydro-1,3-dioxo-2H-benz[f]isoindol-2-yl), 1,3-dihydro-1-oxo-2H-benz[f]isoindol-2-yl, 1,3-dihydro-1,3-dioxo-2H-pyrrolo[3,4-b]quinolin-2-yl, and 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinolin-2-yl

The term "aryl" refers to a mono-, bi- or tri-cyclic, substituted or unsubstituted, carbocyclic aromatic group, and to groups consisting of two covalently linked substituted or unsubstituted monocyclic carbocyclic aromatic groups. Illustrative of such groups are phenyl, biphenyl and naphthyl.

The term "heteroaryl" refers to a 5- or 6- membered substituted or unsubstituted aromatic ring containing one or more heteroatoms, and optionally fused to a benzyl or pyridyl ring; and to groups consisting of two covalently linked 5- or 6- membered substituted or unsubstituted aromatic rings each containing one or more heteroatoms; and to groups consisting of a substituted or unsubstituted monocyclic carbocyclic aromatic group covalently linked to a substituted or unsubstituted 5- or 6- membered aromatic rings containing one or more heteroatoms;. Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, 4-([1,2,3]-thiadiazol-4-yl)phenyl and 5-isoxazol-3-ylthienyl.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be (C₁-C₆)alkoxy, phenoxy, hydroxy, mercapto, (C₁-C₆)alkylthio, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, nitro, -COOH, -CONH₂, -COOR^A, -NHCOR^A, -CONHR^A, -NHR^A, -NR^AR^B, or -CONR^AR^B wherein R^A and R^B are independently a (C₁-C₆)alkyl group.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There is at least one potential chiral centre in the compounds according to the invention because of the presence of potentially asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereomers with R or S stereochemistry at each chiral centre. General formula (II), and (unless specified otherwise) all other formulae in this specification are to be understood to include all such stereoisomers and mixtures (for example racemic mixtures) thereof.

In the compounds of the invention, the preferred stereochemistry is in general as follows:

C atom carrying the R₁ and X group = R,

but mixtures in which the above configuration predominates are also contemplated.

In the compounds of the invention:

R₁ may be for example hydrogen; a (C₁-C₆)alkyl, (C₂-C₆)alkenyl, phenyl, substituted phenyl, phenyl(C₁-C₆)alkyl, substituted phenyl(C₁-C₆)alkyl, heterocyclyl, substituted heterocyclyl, heterocyclyl(C₁-C₆)alkyl, or substituted heterocyclyl(C₁-C₆)alkyl group; a group BSO_nA- wherein n is 0, 1 or 2 and B

is hydrogen or a (C₁-C₆)alkyl, phenyl, substituted phenyl, heterocyclyl, substituted heterocyclyl, (C₁-C₆)acyl, phenacyl or substituted phenacyl group, and A represents (C₁-C₆)alkyl; an aryl(C₁-C₆)alkyl group; an amino(C₁-C₆)alkyl; hydroxy(C₁-C₆)alkyl, mercapto(C₁-C₆)alkyl or carboxy(C₁-C₆)alkyl wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl- group amidated; or a (C₁-C₆)alkyl group substituted by maleimido, succinimido, naphthalimido, 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinol-2-yl, carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, di(lower alkyl)amino, carboxy-lower alkanoylamino, pyrrolidino or morpholino. Specific examples of R₁ groups include hydrogen, methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, tert-butyl, 2,2-dimethylpropyl, cyclohexyl, phenyl, hydroxymethyl, 2-methoxyethyl, 2-methylthioethyl, 2-methylsulphonyl, 4-(N,N-dimethylamino)butyl, 4-(N,N-dimethylglycylamino)butyl, allyl, methoxymethyl, phenylmethyl, phthalimidomethyl, 2-phthalimidoethyl, 4-morpholinoethyl, 4-thiomorpholinoethyl, 2-methylthiazol-4-ylmethyl, tetrazol-5-ylmethyl, 6-chloropiperonyl, 1-pyrazolylmethyl, pyrid-3-ylmethyl, 1-methyl-4-imidazolylmethyl, N-methylpyrid-4-yl, 2-(pyrid-3-yloxy)ethyl, methylthiomethyl, benzylthiomethyl or thienylsulphanylmethyl. Presently preferred are compounds in which R₁ is hydrogen, methyl or phenylmethyl.

R₂ may for example be hydrogen, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-hexadecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-heptadecyl, n-octadecyl, n-nonadecyl, n-eicosyl, n-heneicosyl, n-docosyl, n-tricosyl, n-tetracosyl, cyclohexyl, 3-methoxycarbonylpropyl, 3-carboxypropyl, 4-methoxycarbonylbutyl, 5-methoxycarbonylpentyl, 5-carboxypentyl, 4-(4-methoxybenzyl)benzyl, 4-phenoxy-2-chlorobenzyl, 4-([1,2,3]-thiadiazol-4-yl)benzyl, 2-phenyl-1-carboxy-ethyl, propyloxymethyl, propylsulphanyl, 2-(2-methoxyethoxy)ethyl, 2-(2-methoxyethoxy(2-ethoxy))ethyl, 3-(2-methoxyethoxy)propyl, 2-phenoxy-ethyl, 2-(4-methoxy-phenoxy)-ethyl, 2-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 6-carboxyhexyl, 7-carboxyheptyl, or 8-carboxyoctyl. Presently preferred are compounds in which R₂ is hydrogen, n-nonyl, n-decyl, n-dodecyl, n-hexadecyl, 4-phenoxy-

2-chlorobenzyl, 4-([1,2,3]-thiadiazol-4-yl)benzyl, 3-methoxycarbonylpropyl, 5-methoxycarbonylpentyl, 3-carboxypropyl, 5-carboxypentyl, 2-(2-methoxyethoxy(2-ethoxy))ethyl, 3-methoxypropyl, 2-phenoxyethyl, or 2-(4-methoxy-phenoxy)ethyl. Presently most preferred are compounds in which R_2 is hydrogen, n-nonyl, n-decyl, n-dodecyl, 5-methoxycarbonylpentyl, 5-carboxypentyl, 3-methoxypropyl, 3-carboxypropyl, 2-phenoxyethyl, 2-(4-methoxy-phenoxy)ethyl, and 2-(2-methoxyethoxy(2-ethoxy))ethyl.

Z may for example be phenyl, 4-methylphenyl, 4-tert-butylphenyl, 3-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-aminophenyl, 4-N,N-dimethylaminophenyl, 2,4,6-trimethylphenyl, 2,4,6-isopropylphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 4-ethoxyphenyl, 4-n-hexyloxyphenyl, 4-n-butyloxyphenyl, 4-(2-methylbutyloxyphenyl, 4-n-heptyloxyphenyl, 4-benzyloxyoxyphenyl, 4-isopropyloxyphenyl, 4-ethoxyethoxyphenyl, 2,3-dihydrobenzofuran-5-yl, 1-naphthyl, 2-naphthyl, 2-thienyl, 2-acetamido-4-methyl-thiazol-5-yl, 4-acetamidophenyl, 3,5-dimethylisoxazol-5-yl, 2,4-dimethylisoxazol-5-yl, or 2-(isoxazol-5-yl)thien-5-yl. Presently preferred are such compounds in which Z is 4-methylphenyl, 4-methoxyphenyl, 2-acetamido-4-methyl-thiazol-5-yl, 4-acetamidophenyl, or 2-(isoxazol-5-yl)thien-5-yl.

Specific compounds of the invention include those prepared according to the preparative examples below, in particular the following:

N-Hydroxy-2-[[2-(4-methoxy-phenoxy)-ethyl]-(toluene-4-sulfonyl)-amino]-acetamide,

N-Hydroxy-2-[(4-phenoxy-ethyl)-(toluene-4-sulfonyl)-amino]-acetamide,

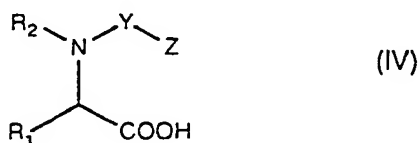
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-nonyl-amino]-acetamide,

2-[-Decyl-(toluene-4-sulfonyl)-amino]-N-hydroxyacetamide,

and salts, solvates or hydrates thereof.

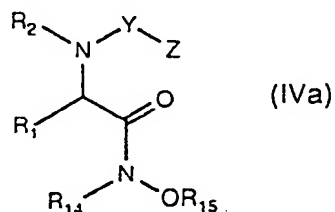
Compounds according to the present invention in which X is a hydroxamic acid group (-CONHOH) may be prepared from compounds of the invention in which X is a carboxylic acid group (-COOH). That process, which forms another aspect of the invention, comprises:

- (a) causing an acid of general formula (IV)



or an activated derivative thereof to react with hydroxylamine, O-protected hydroxylamine, N,O-diprotected hydroxylamine, or a salt thereof, R_1 , R_2 , Y and Z being as defined in general formula (II) except that any substituents in R_1 , R_2 , Y and Z which are potentially reactive with hydroxylamine, O-protected hydroxylamine, N,O-diprotected hydroxylamine or their salts may themselves be protected from such reaction, then removing any protecting groups from the resultant hydroxamic acid moiety and from any protected substituents in R_1 , R_2 , Y and Z; or

- (b) deprotecting a diprotected hydroxamic acid derivative of formula (IVa)



in which R_1 , R_2 , Y and Z are as defined in general formula (II), R_{14} is an amino protecting group and R_{15} is a hydroxyl protecting group.

For method (a) conversion of (IV) to an activated intermediate such as the

pentafluorophenyl, hydroxysuccinyl, or hydroxybenzotriazolyl ester may be effected by reaction with the appropriate alcohol in the presence of a dehydrating agent such as dicyclohexyl dicarbodiimide (DCC), N,N-dimethylaminopropyl-N'-ethyl carbodiimide (EDC), or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ).

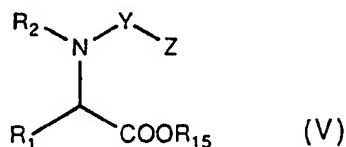
Protecting groups as referred to above are well known per se, for example from the techniques of peptide chemistry. Amino groups are often protectable by benzyloxycarbonyl, t-butoxycarbonyl or acetyl groups, or in the form of a phthalimido group. Hydroxy groups are often protectable as readily cleavable ethers such as the t-butyl or benzyl ether, or as readily cleavable esters such as the acetate. Carboxy groups are often protectable as readily cleavable esters, such as the t-butyl or benzyl ester.

Examples of O-protected hydroxylamines for use in method (a) above include O-benzylhydroxylamine, O-4-methoxybenzylhydroxylamine, O-trimethylsilylhydroxylamine, and O-tert-butoxycarbonylhydroxylamine.

Examples of O,N-diprotected hydroxylamines for use in method (a) above include N,O-bis(benzyl)hydroxylamine, N,O-bis(4-methoxybenzyl)hydroxylamine, N-tert-butoxycarbonyl-O-tert-butyltrimethylsilylhydroxylamine, N-tert-butoxycarbonyl-O-tetrahydropyranylhydroxylamine, and N,O-bis(tert-butoxycarbonyl)hydroxylamine.

For method (b) suitable protecting groups R_{14} and R_{15} are benzyl and substituted benzyl (eg 4-methoxybenzyl). Such protecting groups may be removed by hydrogenolysis, while the 4-methoxybenzyl group may also be removed by acid hydrolysis.

Compounds according to the present invention in which X is a carboxylic acid group -COOH may be prepared by a process comprising hydrolysis of a compound of formula (V):



wherein R_1 , R_2 , Y and Z are as defined in general formula (II), and R_{15} is a carboxy protecting group. Protected carboxy groups include readily cleavable esters, such as the tert-butyl or benzyl ester.

Compounds of formula (V) may be prepared by alkylation of the amino nitrogen of a sulfonamide of formula (VI) with an amine alkylating agent of formula (VII):



wherein R_1 , R_2 , and Z are as defined in general formula (II) except that any substituents in R_1 , R_2 , and Z, which are potentially reactive in the alkylation reaction may themselves be protected from such reaction, R_{15} is as defined for formula (V), and L is a leaving group. Leaving groups L for the alkylation of (VI) by (VII) are well known in the art and include halogen atoms (such as bromine) and triflate.

Sulfonamides of formula (VI) may be prepared by standard methods, including the reaction of an amine of formula (VIII) with an activated sulfonic acid of formula (IX):



wherein R_2 , and Z are as defined in general formula (II). Suitable activated derivatives of (IX) for condensation with (VIII) include the sulfonyl chloride.

As mentioned above, compounds of formula (II) are useful in human or veterinary medicine since they are active as inhibitors of MMPs.

Accordingly in another aspect, this invention concerns:

- (i) a method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound as defined with respect to formula (II) above; and
- (ii) a compound as defined with respect to formula (II) for use in human or

veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs; and

(iii) the use of a compound as defined with respect to formula (II) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs.

Diseases or conditions mediated by MMPs include those involving tissue breakdown such as bone resorption, inflammatory diseases, dermatological conditions and tumour invasion by secondary metastases, in particular rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration and tumour invasion by secondary metastases, tumour growth, tumour angiogenesis, multiple sclerosis, psoriasis, proliferative retinopathy, neovascular glaucoma, ocular tumour, angiofibroma and hemangioma.

In a further aspect of the invention there is provided a pharmaceutical or veterinary composition comprising a compound of formula (II) together with a pharmaceutically or veterinarily acceptable excipient or carrier.

One or more compounds of general formula (II) may be present in the composition together with one or more excipient or carrier.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral

liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

The dosage unit involved in oral administration may contain from about 1 to 250mg, preferably from about 25 to 250mg of a compound of the invention. A suitable daily dose for a mammal may vary widely depending on the condition of the patient. However, a dose of a compound of general formula I of about 0.1 to 300mg/kg body weight, particularly from about 1 to 100mg/kg body weight may be appropriate.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceuticals such as the British Pharmacopoeia.

For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The dosage for topical administration will of course depend on the size of the area being treated. For the eyes, each dose may typically be in the range from 10 to 100mg of the drug.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

For use in the treatment of rheumatoid arthritis, the drug can be administered by the oral route or by injection intra-articularly into the affected joint. The daily dosage for a 70kg mammal may be in the range 10mgs to 1gram.

The Preparative Example which follows describes the preparation of a compound which is not part of the invention, but the process conditions and preparative techniques employed are equally applicable to the preparation of the compounds of the invention having similar structures.

Examples 1 to 17 which follow illustrate embodiments of the invention but are not intended to limit the scope in any way. The amino acids used in the examples were commercially available or were prepared according to literature procedures.

The following abbreviations have been used throughout:

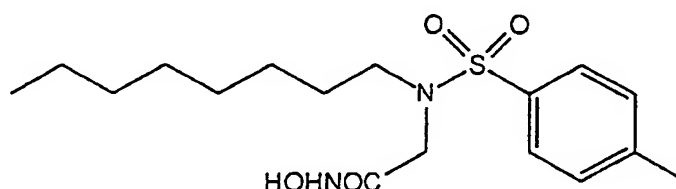
DIPE	Diisopropyl ether
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC	N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
HOBt	1-Hydroxybenzotriazole
LDA	Lithium N,N-diisopropylamide
LHMDS	Lithium hexamethyldisilazide (lithium N,N-bis(trimethylsilyl)amide)
NMM	N-Methylmorpholine
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography

¹H and ¹³C NMR spectra were recorded using a Bruker AC 250E spectrometer at

250.1 and 62.9 MHz, respectively. Elemental microanalyses were performed by CHN Analysis Ltd., Alpha House, Countesthorpe Road, South Wigston, Leicester LE8 2PJ, UK or by MEDAC Ltd, Department of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PH.

Preparative Example

N-Hydroxy-2-[octyl-(toluene-4-sulfonyl)amino]-acetamide



STEP A:

N-octyl-toluene-4-sulfonamide

A solution of toluene-4-sulfonyl chloride (5.0 g, 0.026 mol) in dry dichloromethane (150 ml) was cooled to 0°C during the dropwise addition of n-octylamine (9.6 ml, 0.058 mol) with stirring over 4 minutes. The reaction mixture was then allowed to stir for 30 minutes before being diluted with dichloromethane (200 ml) and water (200 ml). The organic layer was separated and washed consecutively with 1M HCl, 0.5 M Na₂CO₃ and brine before being dried over anhydrous Na₂SO₄. The solution was filtered and concentrated *in vacuo* to a crude solid which was purified by flash chromatography (silica gel, 11% ethyl acetate in hexane) to give the title compound as a white solid (7.0 g, 94%). This material was then used immediately in the next step.

STEP B:

[Octyl-(toluene-4-sulfonyl)amino]-acetic acid *tert*-butyl ester

N-Octyl-toluene-4-sulfonamide (7.0 g, 0.025 mol) was dissolved in dry THF (200

ml) and cooled to -78°C . A 1M solution of LHMDs in THF (27.2 ml, 0.028 mol) was then added over 10 minutes. The reaction mixture was allowed to warm to -40°C with stirring over 30 minutes. Neat *tert*-butyl bromoacetate (4.8 ml, 0.03 mol) was added over 5 minutes and the reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl (200 ml) and ethyl acetate (200 ml). The organic layer was separated and washed consecutively with 1M HCl, 0.5M Na_2CO_3 and brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography (silica gel, 6% ethyl acetate in hexane) to give the title compound as a white solid (5.2 g, 53%). ^1H NMR: δ (CDCl_3), 7.72 (2H, d, $J = 8.3$ Hz), 7.27 (2H, d, $J = 8.4$ Hz), 3.94 (2H, s), 3.23 (2H, dd, $J = 7.5, 7.6$ Hz), 2.42 (3H, s), 1.60 - 1.42 (2H, m), 1.39 (9H, s), 1.34 - 1.17 (10H, m), 0.88 (3H, t, $J = 6.9$ Hz).

STEP C:

[Octyl-(toluene-4-sulfonyl)amino]-acetic acid

An ice-cooled solution of [octyl-(toluene-4-sulfonyl)amino]-acetic acid *tert*-butyl ester (5.2 g, 0.013 mol) in dichloromethane (50 ml) was further diluted by the addition of 25% TFA in dichloromethane (200 ml). The reaction mixture was stored at 4°C overnight. Solvents were removed under reduced pressure and the residue was azeotroped with toluene. The resulting crude oil was purified by flash chromatography (silica gel, 10% methanol in dichloromethane) to give the title compound as a white solid (4.4 g, 99%). ^1H NMR: δ (CDCl_3), 9.77 (1H, br s), 7.71 (2H, d, $J = 8.3$ Hz), 7.25 (2H, d, $J = 8.2$ Hz), 4.00 (2H, br s), 3.19 (2H, dd, $J = 7.4, 7.7$ Hz), 2.38 (3H, s), 1.50 - 1.30 (2H, m), 1.30 - 1.05 (10H, m) and 0.85 (3H, t, $J = 6.6$ Hz).

STEP D:

N-Benzyloxy-2-[octyl-(toluene-4-sulfonyl)amino]-acetamide

[Octyl-(toluene-4-sulfonyl)amino]-acetic acid (4.0 g, 0.012 mol) was taken up in

DMF (150 ml) and treated at room temperature with NMM (1.55 ml, 0.014 mol) followed by EDC (2.92 g, 0.015 mol). The reaction mixture was allowed to stir for 15 minutes at room temperature before the addition of HOBt (2.1 g, 0.016 mol). The reaction mixture was left to stir for a further 20 minutes before a mixture of O-benzylhydroxylamine hydrochloride (1.87 g, 0.012 mol) and NMM (2.6 ml, 0.024 mol) in DMF (50 ml) was added. The reaction mixture was allowed to stir at room temperature for a further 48 h. The DMF was removed under reduced pressure and the resulting crude oil was dissolved in ethyl acetate (200 ml). The solution was washed consecutively with 1M HCl, 0.5M Na₂CO₃ and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (silica gel, 10% methanol in dichloromethane) to give an oil which was further purified by flash chromatography (silica gel, 20% ethyl acetate in hexane) to give the title compound as a white solid (1.91 g, 37%). ¹H NMR: δ (CDCl₃), 9.39 (1H, br s), 7.65 (2H, d, J = 8.2 Hz), 7.45 - 7.20 (7H, m), 4.91 (2H, s), 3.67 (2H, br s), 3.07 (2H, dd, J = 7.5, 7.9 Hz), 2.40 (3H, s), 1.50 - 1.33 (2H, m), 1.31 - 1.10 (10H, m) and 0.86 (3H, t, J = 6.5 Hz).

STEP E:

N-Hydroxy-2-[octyl-(toluene-4-sulfonyl)amino]-acetamide

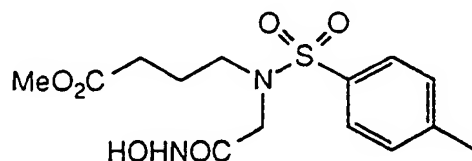
N-Benzylloxy-2-[octyl-(toluene-4-sulfonyl)amino]-acetamide (1.91 g, 0.0043 mol) was taken up in ethanol (150 ml), and 10% palladium on charcoal (800 mg) was added. Hydrogen gas was bubbled through the mixture for 2 hours at room temperature. The catalyst was removed by filtration and the solvent was removed under reduced pressure to give a crude solid which was purified by recrystallization from ethyl acetate/hexane (940 mg, 61%). m.p. 89 °C; ¹H-NMR; δ (CDCl₃), 7.69 (2H, d, J = 8.2 Hz), 7.32 (2H, d, J = 8.2 Hz), 3.76 (2H, s), 3.15 (1H, d, J = 7.6 Hz), 3.12 (1H, d, J = 7.9 Hz), 2.43 (3H, s), 1.58 - 1.41 (2H, m), 1.35 - 1.15 (10H, m) and 0.86 (3H, t, J = 6.4 Hz). ¹³C-NMR; δ (CDCl₃), 166.6, 144.2, 134.6, 129.9, 127.4, 50.7, 49.9, 31.6, 29.1, 29.0, 27.9, 26.6, 22.6, 21.5 and 14.0; IR (CDCl₃), ν_{max} 3413, 2929, 2858, 1682, 1467, 1401, 1346, 1162 and 1091 cm⁻¹.

Found: C 57.27, H 7.87, N 7.95%; $C_{17}H_{28}N_2O_4S$ requires C 57.28, H 7.92, N 7.86%.

The compounds of the following Examples 1 to 15 were prepared according to methods described in the above Preparative Example.

EXAMPLE 1

4-[Hydroxycarbamoylmethyl-(toluene-4-sulfonyl)-amino]-butyric acid methyl ester

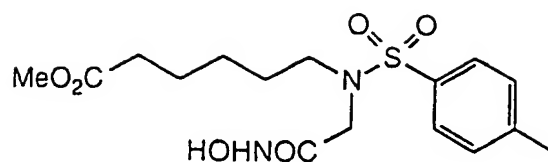


White solid. m.p. 90 - 91°C. 1H -NMR; δ (CD_3OD), 7.63 (2H, d, $J = 8.3$ Hz), 7.28 (2H, d, $J = 8.3$ Hz), 3.67 (2H, s), 3.54 (3H, s), 3.12 (3H, t, $J = 7.1$ Hz), 2.32 (3H, s), 2.32 - 2.25 (2H, m) and 1.77 - 1.68 (2H, m). ^{13}C -NMR; δ (CD_3OD), 175.2, 167.8, 145.2, 137.2, 130.8, 128.6, 52.0, 49.9, 31.4, 24.1 and 21.4. IR (KBr) ν_{max} 3231, 2948, 1738, 1651, 1334 and 1159 cm^{-1} . Found C 48.61, H 5.83, N 7.93%; $C_{14}H_{20}N_2O_6S$ requires C 48.83, H 5.85, N 8.13%.

EXAMPLE 2

6-[Hydroxycarbamoylmethyl-(toluene-4-sulfonyl)-amino]-hexanoic acid methyl ester

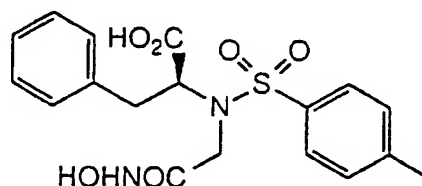
24



Off-white solid. m.p. 77 - 78°C. $^1\text{H-NMR}$; δ (CD_3OD), 7.63 (2H, d, $J = 8.3$ Hz), 7.28 (2H, d, $J = 8.3$ Hz), 3.67 (2H, s), 3.54 (3H, s), 3.06 (2H, t, $J = 7.4$ Hz), 2.32 (3H, s), 2.17 (2H, t, $J = 7.4$ Hz), 1.52 - 1.39 (4H, m) and 1.22 - 1.10 (2H, m). $^{13}\text{C-NMR}$; δ (CD_3OD), 175.7, 167.8, 145.1, 137.3, 130.8, 128.5, 51.9, 50.3, 34.5, 28.4, 27.0, 25.4 and 21.4. IR (KBr) ν_{max} 3250, 2945, 1731, 1649, 1332, 1156, 657 and 558 cm^{-1} . Found C 51.28, H 6.49, N 7.45%; $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_6\text{S}$ requires C 51.60, H 6.50, N 7.52%.

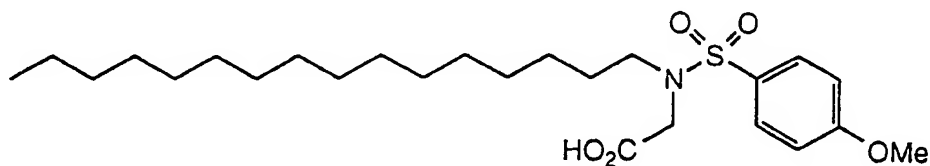
EXAMPLE 3

2-[Hydroxycarbonylmethyl-(toluene-4-sulfonyl)-amino]-3-phenyl-propionic acid

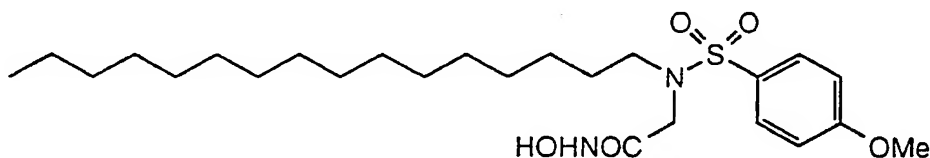


Pale orange foam. $^1\text{H-NMR}$; δ (CDCl_3), 7.46 (2H, d, $J = 8.4$ Hz), 7.32 - 7.26 (7H, m), 7.23 - 7.15 (1H, m), 5.10 - 5.04 (1H, m), 4.59 - 4.52 (1H, d, $J = 19.1$ Hz), 3.87 - 3.80 (1H, d, $J = 19.1$ Hz), 3.30 - 3.17 (2H, m) and 2.41 (3H, s). $^{13}\text{C-NMR}$; δ (CDCl_3), 145.0, 134.7, 133.7, 130.2, 129.8, 128.9, 128.8, 128.6, 127.5, 127.0, 126.7, 59.3, 44.9, 36.4 and 21.4.

EXAMPLE 4

[Hexadecyl-(4-methoxy-benzenesulfonyl)-amino]-acetic acid

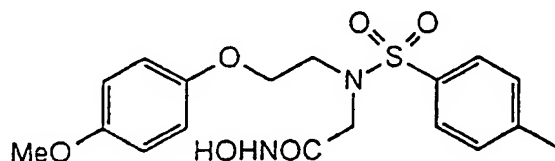
White solid. m.p. 109 - 111°C. ¹H-NMR; δ (CDCl₃), 7.83 - 7.76 (2H, m), 7.03 - 6.96 (2H, m), 4.03 (2H, s), 3.88 (3H, s), 3.21 (2H, dd, J = 7.2 Hz), 1.60 - 1.44 (2H, m), 1.38 - 1.19 (26H, m) and 0.89 (3H, t, J = 6.6 Hz). ¹³C-NMR; δ (CDCl₃), 174.2, 163.0, 131.0, 129.5, 114.1, 55.6, 48.6, 47.8, 31.9, 29.7, 29.5, 29.4, 29.2, 27.8, 26.5, 22.7 and 14.1. IR (KBr) ν_{max} 2917, 2849, 1714, 1257 and 1155 cm⁻¹. Found C 63.58 H 9.28 N 3.03%; C₂₅H₄₃NO₅S . 0.1 H₂O requires C 63.69, H 9.24, N 2.97%.

EXAMPLE 52-[Hexadecyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-acetamide

White crystalline solid. m.p. 115 - 118°C. ¹H-NMR; δ ((CD₃)₂SO), 8.74 (1H, s), 7.60 (2H, d, J = 8.8 Hz), 6.93 (2H, d, J = 8.8 Hz), 3.69 (3H, s), 2.89 (2H, dd, J = 7.2, 7.2 Hz), 1.37 - 0.91 (30H, m) and 0.70 (3H, t, J = 6.4 Hz). ¹³C-NMR; δ ((CD₃)₂SO), 163.2, 161.1, 129.7, 127.9, 112.9, 54.3, 46.9, 45.9, 30.0, 27.8, 27.4, 27.3, 25.9, 24.7, 20.8 and 12.6. IR (KBr) ν_{max} 3189, 3072, 2918, 2851, 1633 and 1599 cm⁻¹. Found C 61.89, H 9.25, N 5.77%; C₂₅H₄₄N₂O₅S requires C 61.95%, H 9.15%, N 5.78%.

EXAMPLE 6

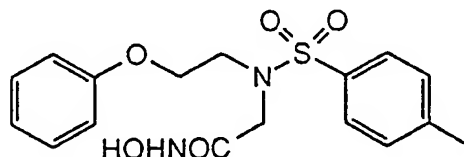
N-Hydroxy-2-[[2-(4-methoxy-phenoxy)-ethyl]-(toluene-4-sulfonyl)-amino]-acetamide



White solid. m.p. 77 - 78 °C. $^1\text{H-NMR}$; δ (CDCl_3), 7.69 (2H, d, $J = 8.3$ Hz), 7.28 (2H, d, $J = 8.4$ Hz), 6.80 (4H, s), 4.11 (2H, t, $J = 5.0$ Hz), 3.91 (2H, s), 3.75 (3H, s), 3.52 (2H, t, $J = 5.1$ Hz) and 2.40 (3H, s). $^{13}\text{C-NMR}$; δ (CDCl_3), 166.2, 154.4, 151.7, 144.4, 134.3, 130.0, 127.4, 115.5, 114.7, 67.0, 55.6, 51.7, 50.3 and 21.5. IR (KBr) ν_{max} 3377, 2927, 1670, 1500, 1333, 1228, 1160 and 1034 cm^{-1} . Found C 54.53, H 5.71, N 6.92%; $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_6\text{S}$ requires C 54.81, H 5.62, N 7.10%.

EXAMPLE 7

N-Hydroxy-2-[(4-phenoxy-ethyl)-(toluene-4-sulfonyl)-amino]-acetamide

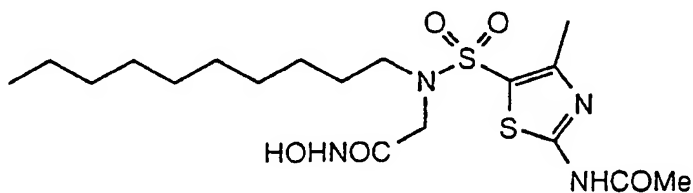


White solid. m.p. 84 - 86°C. $^1\text{H-NMR}$; δ ($\text{CDCl}_3/\text{CD}_3\text{OD}$), 7.59 (2H, d, $J = 8.3$ Hz), 7.22 - 7.02 (4H, m), 6.80 (1H, t, $J = 7.3$ Hz), 6.69 (2H, d, $J = 7.9$ Hz), 4.00 (2H, t, $J = 5.4$ Hz), 3.81 (2H, s), 3.46 (2H, t, $J = 5.4$ Hz) and 2.27 (3H, s). $^{13}\text{C-NMR}$; δ ($\text{CDCl}_3/\text{CD}_3\text{OD}$), 165.9, 157.5, 143.9, 134.6, 129.5, 129.0, 126.9, 120.8, 113.9,

65.8, 50.1, 48.7 and 20.7. IR (CDCl₃) ν_{\max} 3343, 2927, 1681, 1599, 1497, 1350 and 1164 cm⁻¹. Found C 53.43, H 5.39, N 7.37%; C₁₇H₂₀N₂O₅ · 0.9 H₂O requires C 53.64, H 5.77, N 7.36%.

EXAMPLE 8

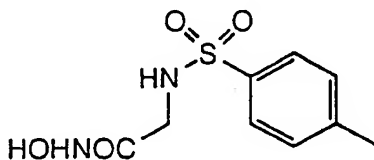
2-[Decyl-(2-acetamido-4-methyl-thiazole-5-sulfonyl)-amino]-acetamide



White solid. ¹H NMR; (CDCl₃), δ 3.83 (2H, m), 3.05 (2H, m), 2.52 (3H, s), 2.35 (3H, s), 1.69 (2H, m), 1.25 - 1.15 (14H, m), 0.87 (3H, t, J = 7.2 Hz).

EXAMPLE 9

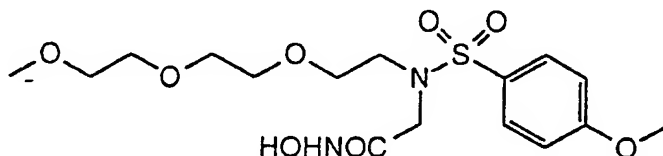
N-Hydroxy-2-(toluene-4-sulfonylamino)-acetamide



Off white solid. ¹H-NMR; δ (CD₃OD), 7.63 (2H, d, J = 8.3 Hz), 7.27 (2H, d, J = 8.2 Hz), 3.36 (2H, s) and 2.32 (3H, s).

EXAMPLE 10

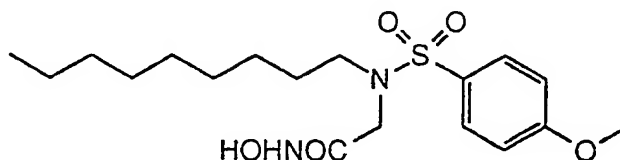
N-Hydroxy-2-((4-methoxy-benzenesulfonyl)-2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl}-amino)-acetamide



Pale yellow wax. $^1\text{H-NMR}$; δ (CD_3OD), 7.70 (2H, m), 6.96 (2H, m), 3.77 (5H, s), 3.59 - 3.37 (10H, br m), and 3.25 (5H, m).

EXAMPLE 11

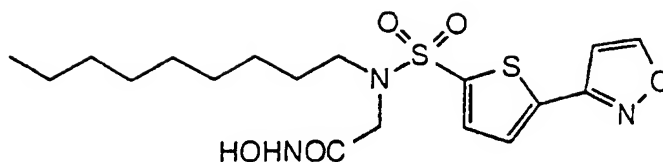
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-nonyl-amino]-acetamide



White solid. $^1\text{H-NMR}$; δ (CD_3OD), 7.70 (2H, d, $J = 1.9$ Hz), 7.68 (2H, d, $J = 1.9$ Hz), 3.77 (3H, s), 3.68 - 3.54 (2H, br m), 3.04 (2H, m), 1.40 (2H, m), 1.15 (10H, m) and 0.79 (3H, m).

EXAMPLE 12

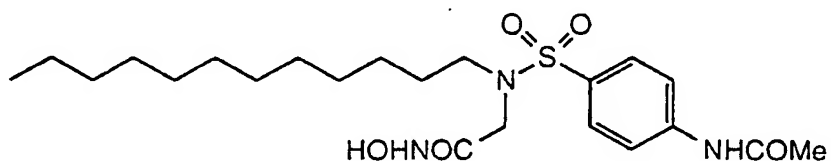
N-Hydroxy-2-[(5-isoxazol-3-yl-thiophene-2-sulfonyl)-nonyl-amino]-acetamide



Pale yellow solid. $^1\text{H-NMR}$; δ (CD_3OD), 8.31 (2H, d, $J = 1.9$ Hz), 7.37 (2H, d, $J = 3.8$ Hz), 7.32 (2H, d, $J = 3.9$ Hz), 6.59 (2H, d, $J = 1.9$ Hz), 3.94 - 3.66 (2H, br m), 2.90 (2H, m), 1.60 (2H, m), 1.18 (10H, m) and 0.79 (3H, m).

EXAMPLE 13

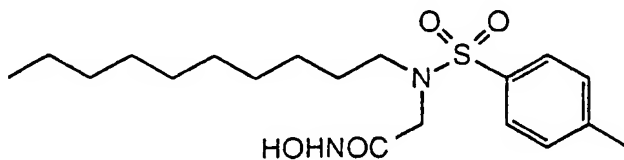
2-[(Acetamidophenyl-4-sulfonyl)-decyl-amino]-N-hydroxyacetamide



Tan solid. $^1\text{H-NMR}$; δ (CD_3OD), 0.79 (3H, t), 1.12 - 1.35 (~16H, m), 2.05 (3H, s), 3.62 (2H, s), 3.92 (2H, t), 7.24 (2H, d), 7.68 (2H, d), 8.43 (1H, s) and 8.91 (1H, s).

EXAMPLE 14

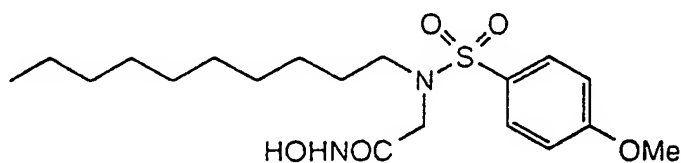
2-[-Decyl-(toluene-4-sulfonyl)-amino]-N-hydroxyacetamide



Yellow wax. $^1\text{H-NMR}$; δ (CDCl_3), 0.86 (3H, t), 1.24 (14H, brn), 1.62 (2H, m), 2.32 (3H, s), 3.62 (2H, s), 4.02 (2H, brt), 7.13 (2H, d), 7.67 (2H, d), 7.81 (1H, s), 8.62 (1H, s). $^{13}\text{C-NMR}$; δ (CDCl_3), 14.1, 21.3, 22.6, 26.2, 28.7, 29.0, 29.2, 29.3, 31.8, 48.4, 125.7, 129.0, 140.6, 141.1.

EXAMPLE 15

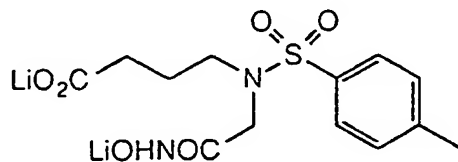
N-Hydroxy-2-[Decyl-4-methoxyphenylsulfonyl-amino]-acetamide



Off-white solid. $^1\text{H-NMR}$; δ (CDCl_3), 0.83 (3H, t), 1.14-1.42 (~16H, m), 3.80 (3H, s), 3.85 (2H, s), 3.92 (2H, t), 6.88 (2H, d), 7.68 (2H, d). $^{13}\text{C-NMR}$; δ (CDCl_3), 14.9, 26.2, 29.3-30.3 (several lines), 31.8, 55.2, 66.2, 113.2, 127.3, 159.6.

EXAMPLE 16

4-[Hydroxycarbamoylmethyl-(toluene-4-sulfonyl)-amino]-butyric acid (dilithium salt)



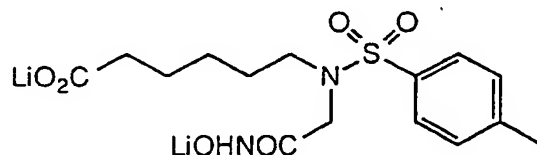
4-[Hydroxycarbamoylmethyl-(toluene-4-sulfonyl)-amino]-butyric acid methyl ester (Example 2) (294 mg, 0.86 mmol) was dissolved in methanol (5 ml) and the solution was cooled to 0°C and stirred during the addition of LiOH (76 mg, 1.80

mmol) in water (5 ml). The solution was stirred for 1 h at 0°C then at room temperature. Further portions of LiOH were added after 6h (18 mg) and 18h (18 mg). Hydrolysis was shown by TLC analysis to be complete after a further 24 h. The solvent was removed under reduced pressure to leave the title compound as a white solid (440 mg, including excess LiOH). $^1\text{H-NMR}$; δ (D_2O), 7.39 (2H, d, $J = 8.3$ Hz), 7.10 (2H, d, $J = 8.4$ Hz), 3.45 (2H, s), 2.89 - 2.78 (2H, m), 2.07 (3H, s), 1.82 - 1.75 (2H, m) and 1.30 - 1.47 (2H, m). $^{13}\text{C-NMR}$; δ (D_2O), 181.5, 180.3, 166.6, 145.0, 137.3, 130.7, 128.6, 50.4, 36.0, 25.9, 24.2 and 21.4. IR (KBr) ν_{max} 3404, 1580, 1423, 1335, 1157, 660 and 548 cm^{-1} .

The following additional compound was prepared according to the method described in Example 19:

EXAMPLE 17

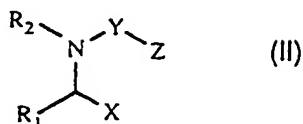
6-[Hydroxycarbonylmethyl-(toluene-4-sulfonyl)-amino]-hexanoic acid (dilithium salt)



Pale yellow solid. $^1\text{H-NMR}$; δ (D_2O), 7.41 (2H, d, $J = 8.3$ Hz), 7.11 (2H, d, $J = 8.4$ Hz), 3.38 (2H, s), 2.82 (2H, m), 2.08 (3H, s), 1.74 (2H, t, $J = 7.4$ Hz), 1.16 - 1.03 (4H, m) and 0.87 - 0.75 (2H, m). $^{13}\text{C-NMR}$; δ (D_2O), 186.3, 165.1, 147.6, 136.6, 132.5, 129.6, 51.5, 51.4, 39.9, 29.1, 28.3, 27.6 and 23.2. IR (KBr) ν_{max} 3240, 2937, 1615, 1580, 1420, 1336, 1157 and 1035 cm^{-1} .

Claims:

1. A compound of general formula (II)



wherein

X represents a -CO₂H or -CONHOH group;

R_1 represents:

(i) the characterising side chain of a natural or non-natural alpha amino acid, in which any functional group present may be protected;

R₂ represents a group Z¹-Q-W- where Z¹ represents hydrogen or an optionally substituted aryl, heteroaryl, non-aromatic heterocyclyl, cycloalkyl, or cycloalkenyl group, and

(i) -Q-W- taken together represent a bond or

(ii) Q represents -O- or -S- and W represents a divalent C₁-C₂₀ straight or branched alkyl or C₂-C₂₀ alkenyl group which

(a) may be interrupted by one or more non-adjacent ether or thioether linkages or -N(R_x)- groups wherein R_x is hydrogen, or C₁-C₆ alkyl, and/or

(b) may carry one or more substituents selected from -OH, -SH, -O(Alk), -S(Alk), halogen, -NH₂, -NH(Alk), -N(Alk)₂, -CO₂H, -CO₂(Alk), -CO(Alk), -CHO, -CONH₂, -CONH(Alk), -CON(Alk)₂, -

(Alk)OH, -(Alk)SH, and -NHCO(Alk) where Alk represents C₁-C₆ alkyl, or

(iii) Q represents a bond and W represents a divalent C₉-C₂₀ straight or branched alkyl or C₂-C₂₀ alkenyl group which

(a) may be interrupted by one or more non-adjacent ether or thioether linkages or -N(R_x)- groups wherein R_x is hydrogen, or C₁-C₆ alkyl, and/or

(b) may carry one or more substituents selected from -OH, -SH, -O(Alk), -S(Alk), halogen, -NH₂, -NH(Alk), -N(Alk)₂, -CO₂H, -CO₂(Alk), -CO(Alk), -CHO, -CONH₂, -CONH(Alk), -CON(Alk)₂, -(Alk)OH, -(Alk)SH, and -NHCO(Alk) where Alk represents C₁-C₆ alkyl, or

(iv) Q represents a bond and W represents a divalent C₁-C₈ straight or branched alkyl group which

(a) carries one or more substituents selected from -SH, -CO₂H, -CO₂(Alk), -CHO, -CONH₂, -CONH(Alk), -CON(Alk)₂, and -(Alk)SH, where Alk represents C₁-C₆ alkyl, and

(b) (in the case where W is C₂-C₈) may be interrupted by one or more non-adjacent ether or thioether linkages or -N(R_x)- groups wherein R_x is hydrogen, or C₁-C₆ alkyl;

Y represents a sulphonyl -(SO₂)- group; and

Z represents an optionally substituted aryl, or heteroaryl group;

or a salt, hydrate or solvate thereof.

2. A compound as claimed in claim 1 wherein R_2 represents

(i) a group Ar-Q-W- in which Ar represents optionally substituted aryl or heteroaryl, Q represents -O- or -S-, and W represents a divalent C_1 - C_{20} straight or branched chain alkyl moiety which may carry one or more substituents selected from OH, OMe, halogen, NH_2 , NMeH, NMe_2 , CO_2H , CO_2Me , COMe, CHO, $CONH_2$, CONHMe, $CONMe_2$, CH_2OH , NHCOMe; or

(ii) a group Ar-Q-W- in which Ar represents optionally substituted aryl or heteroaryl, Q represents a bond, and W represents a divalent C_9 - C_{20} straight or branched chain alkyl moiety may carry one or more substituents selected from OH, OMe, halogen, NH_2 , NMeH, NMe_2 , CO_2H , CO_2Me , COMe, CHO, $CONH_2$, CONHMe, $CONMe_2$, CH_2OH , NHCOMe; or

(iii) a group Ar-Q-W- in which Ar represents optionally substituted aryl or heteroaryl, Q represents a bond, and W represents a divalent C_1 - C_8 straight or branched chain alkyl moiety which carries one or more substituents selected from $-CO_2H$, $-CO_2Me$, $-CHO$, $-CONH_2$, $-CONHMe$, and $-CONMe_2$; or

(v) a cycloalkenyl(C_1 - C_6)alkyl group; or

(vi) a linear saturated C_9 - C_{20} or unsaturated C_2 - C_{20} hydrocarbon chain, which chain

(a) may be interrupted by one or more non-adjacent -O- or -S- atoms or $-N(R_x)-$ groups wherein R_x is hydrogen, methyl or ethyl, and/or

(b) may be substituted with one or more groups selected from (C_1 - C_6)alkyl, OH, OMe, halogen, NH_2 , NMeH, NMe_2 , CO_2H , CO_2Me , COMe, CHO, $CONH_2$, CONHMe, $CONMe_2$, CH_2OH , NHCOMe,

provided that the maximum length of the chain is no more than 28 C, O, S

and N atoms; or

(vii) a linear saturated C₂-C₈ hydrocarbon chain, which chain

(a) is substituted with one or more groups selected from -CO₂H, -CO₂Me, -CHO, -CONH₂, -CONHMe, and -CONMe₂, and

(b) may be interrupted by one or more non-adjacent -O- or -S- atoms or -N(R_x)- groups wherein R_x is hydrogen, methyl or ethyl,

provided that the maximum length of the chain is no more than 28 C, O, S and N atoms.

3. A compound as claimed in claim 1 wherein R₂ represents

(i) a cycloalkenyl(C₁-C₆)alkyl group, or

(ii) a linear saturated C₂-C₈ hydrocarbon chain, which chain

(a) may be interrupted by one or more non-adjacent -O- or -S- atoms or -N(R_x)- groups wherein R_x is hydrogen, methyl or ethyl, and

(b) is substituted with one or more groups selected from -CO₂H, -CO₂Me, -CHO, -CONH₂, -CONHMe, and -CONMe₂, or

(iii) a linear saturated C₉-C₂₀ or unsaturated C₂-C₂₀ hydrocarbon chain, which chain

(a) may be interrupted by one or more non-adjacent -O- or -S- atoms or -N(R_x)- groups wherein R_x is hydrogen, methyl or ethyl, and/or

(b) may be substituted with one or more groups selected from (C₁-C₆)alkyl, OH, OMe, halogen, NH₂, NMeH, NMe₂, CO₂H, CO₂Me,

COMe, CHO, CONH₂, CONHMe, CONMe₂, CH₂OH, NHCOMe,

provided that the maximum length of the chain is no more than 28 C, O, S and N atoms,

4. A compound as claimed in any one of the preceding claims wherein R₁ is hydrogen; a (C₁-C₆)alkyl, (C₂-C₆)alkenyl, phenyl, substituted phenyl, phenyl(C₁-C₆)alkyl, substituted phenyl(C₁-C₆)alkyl, heterocyclyl, substituted heterocyclyl, heterocyclyl(C₁-C₆)alkyl, or substituted heterocyclyl(C₁-C₆)alkyl group; a group BSO_nA- wherein n is 0, 1 or 2 and B is hydrogen or a (C₁-C₆)alkyl, phenyl, substituted phenyl, heterocyclyl, substituted heterocyclyl, (C₁-C₆)acyl, phenacyl or substituted phenacyl group, and A represents (C₁-C₆)alkyl; an aryl(C₁-C₆)alkyl group; an amino(C₁-C₆)alkyl; hydroxy(C₁-C₆)alkyl, mercapto(C₁-C₆)alkyl or carboxy(C₁-C₆)alkyl wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl- group amidated; or a (C₁-C₆)alkyl group substituted by maleimido, succinimido, naphthalimido, 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinol-2-yl, carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, di(lower alkyl)amino, carboxy-lower alkanoylamino, pyrrolidino or morpholino.

5. A compound as claimed in any of claims 1 to 3 wherein R₁ is hydrogen, methyl, ethyl, propyl, iso-propyl, butyl, isobutyl, tert-butyl, 2,2-dimethylpropyl, cyclohexyl, phenyl, hydroxymethyl, 2-methoxyethyl, 2-methylthioethyl, 2-methylsulphonyl, 4-(N,N-dimethylamino)butyl, 4-(N,N-dimethylglycylamino)butyl, allyl, methoxymethyl, phenylmethyl, phthalimidomethyl, 2-phthalimidoethyl, 4-morpholinoethyl, 4-thiomorpholinoethyl, 2-methylthiazol-4-ylmethyl, tetrazol-5-ylmethyl, 6-chloropiperonyl, 1-pyrazolylmethyl, pyrid-3-ylmethyl, 1-methyl-4-imidazolylmethyl, N-methylpyrid-4-yl, 2-(pyrid-3-yloxy)ethyl, methylthiomethyl, benzylthiomethyl or thienylsulphanylmethyl.

6. A compound as claimed in any of claims 1 to 3 wherein R₁ is hydrogen, methyl or phenylmethyl.

7. A compound as claimed in any of the preceding claims wherein R_2 is hydrogen, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-hexadecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-heptadecyl, n-octadecyl, n-nonadecyl, n-eicosyl, n-heneicosyl, n-docosyl, n-tricosyl, n-tetracosyl, cyclohexyl, 3-methoxycarbonylpropyl, 3-carboxypropyl, 4-methoxycarbonylbutyl, 5-methoxycarbonylpentyl, 5-carboxypentyl, 4-(4-methoxybenzyl)benzyl, 4-phenoxy-2-chlorobenzyl, 4-([1,2,3]-thiadiazol-4-yl)benzyl, 2-phenyl-1-carboxy-ethyl, propyloxymethyl, propylsulphanyl, 2-(2-methoxyethoxy)ethyl, 2-(2-methoxyethoxy(2-ethoxy))ethyl, 3-(2-methoxyethoxy)propyl, 2-phenoxy-ethyl, 2-(4-methoxy-phenoxy)-ethyl, 2-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 6-carboxyhexyl, 7-carboxyheptyl, or 8-carboxyoctyl.

8. A compound as claimed in any of claims 1 to 6 wherein R_2 is hydrogen, n-nonyl, n-decyl, n-dodecyl, n-hexadecyl, 4-phenoxy-2-chlorobenzyl, 4-([1,2,3]-thiadiazol-4-yl)benzyl, 3-methoxycarbonylpropyl, 5-methoxycarbonylpentyl, 3-carboxypropyl, 5-carboxypentyl, 2-(2-methoxyethoxy(2-ethoxy))ethyl, 3-methoxypropyl, 2-phenoxyethyl, or 2-(4-methoxy-phenoxy)ethyl.

9. A compound as claimed in any of claims 1 to 6 wherein R_2 is hydrogen, n-nonyl, n-decyl, n-dodecyl, 5-methoxycarbonylpentyl, 5-carboxypentyl, 3-methoxypropyl, 3-carboxypropyl, 2-phenoxyethyl, 2-(4-methoxy-phenoxy)ethyl, or 2-(2-methoxyethoxy(2-ethoxy))ethyl.

10. A compound as claimed in any of the preceding claims wherein Z is phenyl, 4-methylphenyl, 4-tert-butylphenyl, 3-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-aminophenyl, 4-N,N-dimethylaminophenyl, 2,4,6-trimethylphenyl, 2,4,6-isopropylphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 4-ethoxyphenyl, 4-n-hexyloxyphenyl, 4-n-butyloxyphenyl, 4-(2-methylbutyloxyphenyl, 4-n-heptyloxyphenyl, 4-benzyloxyoxyphenyl, 4-isopropyloxyphenyl, 4-ethoxyethoxyphenyl, 2,3-dihydrobenzofuran-5-yl, 1-naphthyl, 2-naphthyl, 2-thienyl, 2-acetamido-4-methyl-thiazol-5-yl, 4-acetamidophenyl, 3,5-dimethylisoxazol-5-yl, 2,4-dimethylisoxazol-5-yl, or 2-(isoxazol-5-yl)thien-5-yl.

11. A compound as claimed in any of claims 1 to 9 wherein Z is 4-methylphenyl, 4-methoxyphenyl, 2-acetamido-4-methyl-thiazol-5-yl, 4-acetamidophenyl, or 2-(isoxazol-5-yl)thien-5-yl.

12. A compound selected from the group consisting of

N-Hydroxy-2-[[2-(4-methoxy-phenoxy)-ethyl]-(toluene-4-sulfonyl)-amino]-acetamide,

N-Hydroxy-2-[(4-phenoxy-ethyl)-(toluene-4-sulfonyl)-amino]-acetamide,

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-nonyl-amino]-acetamide,

2-[-Decyl-(toluene-4-sulfonyl)-amino]-N-hydroxyacetamide,

and salts, solvates or hydrates thereof.

14. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Intern. Application No PCT/GB 95/01465		
A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07C311/19 C07C311/29 C07D277/36 C07D413/04 C07C311/46 A61K31/18		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07C		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE CHEMICAL SOCIETY, 1946 LETCHWORTH, GB, pages 30-36, G.R. CLEMO, ET AL.: 'The constitution of psi-santonin' see page 35, last paragraph <div style="text-align: center;">--- -/--</div>	1,4-6, 10,11
<div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. </div> <div> <input checked="" type="checkbox"/> Patent family members are listed in annex. </div> </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>* "A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>* "E" earlier document but published on or after the international filing date</p> <p>* "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>* "O" document referring to an oral disclosure, use, exhibition or other means</p> <p>* "P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>* "&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center;">29 September 1995</div>		Date of mailing of the international search report <div style="text-align: center;">10. 10. 95</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer <div style="text-align: center;">English, R</div>

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/GB 95/01465

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 59, no. 4, 19 August 1963 Columbus, Ohio, US; abstract no. 3824a, K. KONDO, ET AL.: 'N-Arylglycine chemotherapeutics. IV. Syntheses of (p-methoxyphenylamino)acetohydroxamic acid, (p-methoxyphenylamino)acetamide, and their derivatives' see abstract, compound V & YAKUGAKU ZASSHI, 1963, 83, 130-134 ---	1,4-6,10
X	CHEMICAL ABSTRACTS, vol. 70, no. 19, 12 May 1969 Columbus, Ohio, US; abstract no. 88228j, N. YONEDA, ET AL.: 'Reaction of L-alpha-tosylamido-beta-propiolactone. I. Synthesis, reactions with amines and derivation to L-serine' page 396; see abstract & YAKUGAKU ZASSHI, 1969, 89(1), 98-103 ---	1,4,5, 7-11
A	EP,A,0 236 872 (HOFMANN-LA ROCHE) 16 September 1987 cited in the application see page 2 ---	1,14
P,A	EP,A,0 606 046 (CIBA-GEIGY) 13 July 1994 cited in the application see page 2; claims; examples -----	1,14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB95/01465

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1-14 have been searched incompletely.
Please see attached sheet ./.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int: International Application No

PCT/GB 95/01465

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-236872	16-09-87	AU-B- 588437	14-09-89
		AU-B- 6990287	17-09-87
		CA-A- 1314655	16-03-93
		DE-A- 3782751	07-01-93
		IE-B- 60128	01-06-94
		JP-B- 6029228	20-04-94
		JP-A- 62230757	09-10-87
		US-A- 4996358	26-02-91
EP-A-606046	13-07-94	AU-B- 5265593	04-05-95
		CA-A- 2112779	07-07-94
		FI-A- 940012	07-07-94
		JP-A- 6256293	13-09-94
		NO-A- 940038	07-07-94